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Review Article

Regulatory aspects for Biologic Product licensing in Australia

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Abstract

The TG Act defines biological as product made, from or containing, human cells or human tissues, lives animal organs, cells or tissues, and that is used to treat or prevent disease or injury, Diagnose a condition of a person and Alter the physiological processes of a person.

The Australian Regulatory Guidelines for Biologicals (ARGB) provide the keen information for manufacturers, sponsors, professionals in healthcare and also to public about the use of human cells and tissues based therapeutic goods, live animal cells, organs and tissues (1). These all products are Biologicals. This guideline is specially written for general public. If you are a sponsor or manufacture, this will:

• Explains the biological regulatory framework is applies to manufacturer’s product and their exemption conditions (1).
• Explains the Australian regulatory requirements for supplying of Biologicals
• Explains what is required for the market authorization as per TGA especially for Biologicals.

Keywords: Biologicals, TGA, ARGB, Therapeutic Goods.

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1. Introduction

Biologicals Regulatory Framework

The Biologicals Regulatory Framework is the term for legislation that came into force in 2011 for the regulation of human cells and tissue-based, or live animal organ, cell and tissue-based products as a distinct group of therapeutic goods called ‘Biologicals’. The framework is administered by the Therapeutic Goods Administration (TGA), who has produced this document-the Australian Regulatory Guidelines for Biologicals (ARGB)-to inform manufacturers, sponsors, healthcare professionals and all other interested parties about the framework (2).

The Key features of the framework are listed below:

The Biologicals Regulatory Framework provides a comprehensive system of assessment and controls that must be completed before products are allowed to be marketed in Australia (premarket), and follow-up and further controls after they are marketed (post-marketed) (3).

Before Biologicals can be legally imported, exported, manufactured or supplied in Australia, they must be:

• Included on the ARTG (Australian Register of Therapeutic Goods)
  Or
• Otherwise exempted, approved or authorized.

The Biologicals regulatory framework allows for four classes of Biologicals based on the risk posed by the products, which are in turn related to:

• The methods used to prepare and process the product during their manufacture
  And
• Whether their intended use is the same as their usual biological function.

Key benefits of the Biologicals Regulatory Framework

• Minimize the risk of infectious disease transmission
• Ensure the level of regulation applied matches the level of risk
• Provide a more flexible framework to respond to changes in technology than has been the case under previous arrangements
• Increase International harmonization of therapeutic goods regulation
• Reduce the ambiguity about what was included or excluded from regulation through the use of consistent terminology (2).

**Products Regulated as Biologicals under the Biologicals framework (4)**

To be included in the Biologicals Regulatory Framework, products must:

• Be therapeutic goods (as defined in the TG Act)
• Not be an ‘excluded good’
• Either meet the definition of a biological or are specified by legislative instrument to be a biological
• Not be specified in the Therapeutic Goods Determination ‘Things that are not Biologicals’

Biologicals currently only refer to human cells and tissues, or live animal cells, tissues and organs, and not to:

• Tissues or cells from non-human or non-animal biological sources (e.g. bacteria)
• Medicines made using biological or biotechnology processes (e.g. non-cellular vaccines, insulin) (4).

The following Biologicals are currently included in the regulatory framework:

• Human tissue therapy products (e.g. skin, tissues, bone for grafting)
• Processed human tissues (e.g. demineralised bone, collagen)
• Human cellular therapy products (e.g. cartilage cells, cultured skin cells)
• Immunotherapy products containing human cells
• Genetically modified human cellular products.
• Live animal cells, tissue and organs (e.g. pancreatic islet cells isolated from pigs)

**Products not covered by the Biologicals framework (5, 6)**

• Fresh viable human organs, or parts of human organs, for direct donor-to-host transplantation and used in accordance with applicable laws and standards
• Fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution (e.g. bone marrow cells and cord blood)
• Reproductive tissue (e.g. sperm, eggs, embryos for in vitro fertilisation and other assisted reproductive technologies) that are ‘unmanipulated’ (i.e. they have not been processed in any way apart from freezing).

**Australian regulatory guidelines for Biologicals (ARGB) (7, 2):** The ARGB:

• Explains legislative requirements outlined in the regulatory framework for Biologicals
• Provides information about the supply and use of human cell and tissue based therapeutic goods, living cells of animal based
2. Regulatory framework for Biologicals (4, 7)

It provides the legislative basis for the regulation of human tissue and also the cell derived products and living animal cells, tissue or organs that are supplied or exported in Australia. This was commenced on 31 May 2011, following a recommendation from Commonwealth, state, and Territory health ministers to improve the regulation of human tissues and cell based therapies. All products need to comply with the requirements made under this legislation (4). The framework applies different levels of regulation to products based on the risks associated with their use. It is designed to be flexible enough to accommodate emerging technologies (7).

Table 1 Classification of Biologicals and their level of risk (8, 9)

<table>
<thead>
<tr>
<th>Definitions from the TG Regulations</th>
<th>Meaning</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 biological means a biological that is declare in regulations as a class 1 biologicals.</td>
<td>This has been designated Class 1 and is specified in Schedule 16 of the TG regulations.</td>
<td>Low</td>
</tr>
<tr>
<td>Class 2 biologicals means a biologicals that is:</td>
<td>It is prepared using simple methods, as stated for minimal manipulation method.</td>
<td>Low</td>
</tr>
<tr>
<td>a. Both:</td>
<td>• Processed using only one or more of the actions of minimal manipulation.</td>
<td></td>
</tr>
<tr>
<td>• For homologous use.</td>
<td>• Declared in the regulations as a class 2 biologicals.</td>
<td></td>
</tr>
<tr>
<td>b. Declared in the regulations as a class 2 biologicals.</td>
<td>It is prepared using simple methods, as stated for minimal manipulation method.</td>
<td></td>
</tr>
<tr>
<td>Class 3 biologicals means a biological that is:</td>
<td>• It is prepared using more complex methods, such as enzymatic dissociation.</td>
<td>Medium</td>
</tr>
<tr>
<td>a. Processed:</td>
<td>• These methods do not change the biological properties of the product.</td>
<td></td>
</tr>
<tr>
<td>• Using a method in addition to any of the minimal manipulation.</td>
<td>• In a way that does not change in inherent biochemical or immunological property.</td>
<td></td>
</tr>
<tr>
<td>• In a way that does not change in inherent biochemical or immunological property.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Declared in the regulations as a class 3 biologicals.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 4 biological means a biologicals that is:</td>
<td>• It is prepared using more complex methods, as for class 3.</td>
<td>High</td>
</tr>
<tr>
<td>a. Processed:</td>
<td>• The method have used have changed the biological properties of the product.</td>
<td></td>
</tr>
<tr>
<td>• Using a method in addition to any of the actions of minimal manipulation.</td>
<td>• In a way that changes an inherent biochemical, immunological property.</td>
<td></td>
</tr>
</tbody>
</table>
Different forms for the Biologicals industry (2)

Followings are the forms for Biologicals industry:

- **Exceptional release of a biological**: Access to the request form and instructions are within guidance document.
- **Request for advice on Biologicals**: Information required to be submitted when requesting advice on the classification of Biologicals.
- **TGA business service forms**: Forms for sponsors, agents, manufacturers to apply for access to TGA business services.
- **Notification of a change in sponsorship**: Use to notify of a change in sponsorship of ARTG entry.
- **Proposal for new Australian cell & Tissue Name (ACN) application form**: Use this form when applying for new cell and tissue name is Australia.
- **Biologicals, human blood and blood components report form**: Use to report recalls of human blood and biological products that are derived from human or live animal materials (2).

Legislation of Biologicals (2, 3, 9): The regulations of Biologicals are specified in:

- Therapeutic goods act 1989
- Therapeutic goods regulations 1990
- Therapeutic goods (human cells, tissues and organs) determination 2018
- Therapeutic goods (charges) regulations 1990

Post market requirements for Biologicals (3,7)

- ADR reporting
- Product recall initiation
- Hazard alert
- Australian regulatory guidelines for advertising therapeutic goods

3. Standards for Biologicals (2, 11)

- **Default standards**: The Biologicals must comply with the any default standards. Default standards are publicly available standards that are mandated through the Therapeutic Goods Act 1989 and provided by the:
  - British pharmacopoeia
  - European pharmacopoeia
  - US pharmacopoeia

- **Manufacturing principles**: Different manufacturing principles apply to different kinds of Biologicals:
  - Biologicals that contain human cells and tissues, must comply with the Australian code of GMP for human blood and blood components.
  - Biologicals that contain living animal cells, tissues or organs should be complying with PIC/S guide to GMP (2).

- **Product specific standards**: Product specific standards refer to Therapeutic Goods Orders (TGOs) that specify the legal requirements for the different product types, including labelling:
  - Human skin
  - Human ocular tissue
  - Human cardiovascular tissue
To ensure product quality and safety and to minimise risk, a risk-management system must be applied through all stages of the product’s life, from concept or collection to release and clinical use. The risk-management system should guide manufacturers to identify and analyse risks, and to evaluate and control the risks at all stages of the biological product’s life (9). The nature of Biologicals means that they can pose risks that do not apply to other therapeutic goods, such as the risk of infectious disease transmission, or other unforeseen biological reactions (8).

In addition, the diverse range of starting materials and processes used in the manufacture of Biologicals leads to differing levels of risk (11). Consequently, to approve a Class 2, Class 3 or Class 4 biological for inclusion on the ARTG, the TGA will need to determine that risk has been appropriately managed by taking into account the risks specific to the biological, as well as the level of risk imposed by the manufacturing materials and process (5).

5. Conclusion

After the study of Regulatory Aspects for Biologic Product Licensing in Australia, I have come to know about the various regulatory requirements, product licensing and different kinds of applicable forms that are necessary to taken into considerations for the biologic product in Australia.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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